REMARKS

Applicants respectfully request reconsideration of this application, and reconsideration of the Office Action dated September 9, 2003 (Paper No. 23). Upon entry of this Amendment, claims 33, 34, 36, 38, and 40-97 will remain pending in this application with claims 42-54, 60, 61, 63, 68, 69, 71, 72, 75-87 and 90-97 being withdrawn. Claims 35, 37, and 39 have been cancelled and new claim 98 is added. The amendments to the claims and newly added claim 98 are supported by the specification and original claims. Particularly, the amendment to claim 33 finds support at page 17, Example 7 and previous claim 39. No new matter is incorporated by this Amendment. No additional fees are believed to be necessary as a result of the newly added claim.

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Claims 33-41, 55-59, 62, 64-67 and 70 are rejected under 35 U.S.C. §101 as purportedly claiming the same invention as that of claims 1-10, 17-19, 21 and 23 of co-pending application no. 09/519,998. Applicants respectfully traverse this rejection.

The M.P.E.P. teaches, to make a double patenting rejection under 35 U.S.C. §101, the inventions of the two applications must be drawn to identical subject matter. See M.P.E.P. § 804(II). The M.P.E.P. further teaches:

> **A reliable test for double patenting under 35 U.S.C. 101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Is there an embodiment of the invention that falls within the scope of one claim, but not the other? If there is such an embodiment, then identical subject matter is not defined by both claims and statutory double patenting would not exist. MPEP 804(II)(A).**

The claims of the copending application and those of the present application are of different scope. Accordingly, identical subject matter is not claimed by both applications. Hence, the rejection is improper and should be withdrawn. Applicants respectfully request that this rejection be reconsidered and withdrawn.

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Claims 33-41, 54-59, 62, 64-67, 70-74, 88, and 89 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

In the Office Action, it is asserted that the terminology "derivation of" in claim 33 is indefinite. In response, claim 33 has been amended to recite "comprising biotin or a biotin derivative having essentially the same binding function to avidin or streptavidin as biotin." Hence, claim 33 as amended fully complies with 35 U.S.C. §112.

Claim 70 has been amended to recite "wherein compounds 41, 42, and 44 are stabilized against enzymatic cleavage by biotinidase." Thus, claim 70 includes a "." And fully complies with 35 U.S.C. §112.

The Office Action states that it is unclear to what the term "biomolecule" in claims 88 and 89 refers. Applicants note that claim 33, from which claims 88 and 89 depend, includes the following feature, "a biomolecule reactive moiety, coupled to the trifunctional cross-linking moiety, optionally via a third linker, the biomolecule reactive moiety being able to react with a biomolecule to form a covalent bond with the biomolecule." In other words, a moiety that can react and form a covalent bond with a biomolecule is attached to the trifunctional cross-linking moiety in claim 33. Claims 88 and 89 refer to a diagnostic or therapeutic conjugate and method which include a biomolecule being attached to the single molecule reagent defined by claim 33. In short, the biomolecule of claims 88 and 89 is not the same as the biomolecule reactive moiety of claim 33.

The amendments to the claims and above remarks overcome this rejection. Hence, reconsideration and withdrawal of the rejection are respectfully requested.

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Claims 33-35, 39-41, 55-59, 62, 64-67, 73, 74, 88, and 89 are rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Wilbur et al. (WO 97/29114). The Office Action asserts that Wilbur discloses every element of the claimed invention. Applicants respectfully traverse.

As an initial matter, Applicants submit that this rejection is improper since Wilbur does not qualify as prior art under 35 U.S.C. §102(b). To qualify as prior art under 35 U.S.C. §102(b) a document must show, "(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States." *35 U.S.C. § 102(b)*. Wilbur was published August 14, 1997. The present application claims the benefit of PCT/SE98/01345 which was filed on July 7, 1998. Hence, the Wilbur document was neither patented nor described in a printed publication in this or a foreign country more than one year prior to the earliest date to which the present application is entitled. Hence, the rejection is improper and should be withdrawn.

Applicants also provide the following comments with respect to how the claimed invention distinguishes over Wilbur. The present invention refers to trifunctional reagents, which bond covalently to a bio-molecule and are stabilized against biotinidase. In Wilbur, stabilization against biotinidase is only disclosed in connection with a difunctional reagent. Furthermore, introducing a functional reagent does not necessarily mean that the functionality may be introduced in a trifunctional reagent without affecting the affinity due to steric or other structural features. In other words, Wilbur neither teaches nor fairly describes stabilization against biotinidase in connection with a trifunctional reagent.

Wilbur does not teach nor fairly describe the type of reagents disclosed in the present application. Moreover, the treatment modalities in which the difunctional reagents of Wilbur are used are completely different from those of the present invention. Wilbur states on page 17, that a steric group alpha to the amine provides resistance to cleavage by biotinidase and that such a group may include carboxylate etc. However, on top of page 18, Wilbur states that "depending upon the steric bulk of the branching group alpha to the amine (or other) functionality attached to the carboxylate, some reduction in binding affinity for biotin binding proteins may result."

In contrast, Applicants have surprisingly found that, for example, introduction of an aspartyl residue of linker 1, unforeseeably does not effect the binding affinity to avidin and provides, at the same time, full resistance towards enzymatic cleavage by biotinidase as has later been confirmed by Wilbur et. al. (Bioconjugate Chem. 2000,11,569-583 (in particular p. 581, Chart 4) and Bioconjugate. Chem. 2001,12,616-623 (in particular p. 622, Fig. 2), both attached). These excellent properties have also been confirmed in vivo by Wilbur et al. (PCT/SE03/01949). PCT/SE03/01949 discloses *in vivo* data confirming that a trifunctional reagent of the type described in the present invention and comprising, e.g., an aspartyl residue is stable in the blood circulation over at least 96 hours after administration into rats. Furthermore, the stability of the above compound and the excellent binding kinetics have also been confirmed in clinical studies. It is notable that it is not only the bulkiness or sterical features of the biotinidase protecting substituent that determines the combination of retained avidin biding affinity and resistance to biotinidase as revealed by the above publications of Wilbur in WO 97/29114. Thus, the a statement in Wilbur '114, mentioned above and cited in the Office Action actually dissuades a person of ordinary skill in the art from trying to introduce an aspartyl group in the linker 1 molecule. Accordingly, as explained above, Wilbur fails to teach or fairly suggest each and every feature of independent claim 33 and thus cannot anticipate the claimed invention.

The above remarks overcome this rejection. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

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Claims 33-41, 55-59, 62, 64-67, 70, 73, 74, 88, and 89 are rejected under 35 U.S.C. § 103(a) as being obvious based on Wilbur et al. in view of Griffiths (U.S. Pat. No. 5,482,698). Applicants again respectfully traverse.

The deficiencies of Wilbur are discussed above. Griffith fails to remedy these deficiencies. The reagents disclosed by Griffith differ from the reagent of the present invention by the nature of their structure and by the intended use. Moreover, none of the reagents described by Griffith are trifunctional as defined in the present invention.

Those of ordinary skill in the art would not have been motivated to combine the teachings of Wilbur and Griffith as suggested in the Office Action. For example, since Griffith teaches away from any use of a single molecule comprising an "effector agent" (e.g. radionuclide) and "affinity ligand" (e.g. biotin) which is covalently bound to a "biomolecule" (e.g. tumor specific monoclonal antibody), a trifunctional reagent would not be useful in the treatment modalities disclosed by Griffith. Griffith actually teaches away from any treatment modalities where the targeting molecule comprising a therapeutic/detection agent, either alone, or with an affinity label linked to the same targeting molecule, is administered to the patient or used in other context. Instead, Griffith and to a large extent, Wilbur, teach the use of treatment modalities where the targeting molecule, which could be linked to avidin or biotin, is administered to the patient separately from the radionuclide/biotin compound as separate consecutive steps (Griffith by the disclosure of multistep approaches and Wilbur by disclosure of difunctional compounds useful in this context). Hence, there is no teaching in the knowledge gained from the combined documents, which could give any guidance to the reagent according to the present invention.

The above remarks overcome this rejection. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

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Applicants respectfully submit that this Amendment and the above remarks obviate the outstanding objection and rejections in this case, thereby placing the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

Furthermore, if the Examiner deems that this Amendment does not place the application in condition for allowance, the Examiner is respectfully requested to contact Applicants' undersigned representative to discuss any remaining issues.

If any fees are due in connection with the filing of this Amendment, such as fees under 37 C.F.R. §§1.16 or 1.17, please charge the fees to Deposit Account 02-4300; Order No. 033700.005.

Respectfully submitted,

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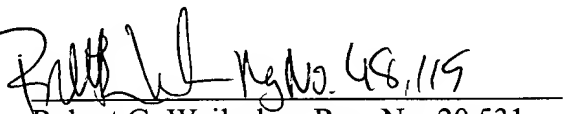
By:  Reg No. 48,115
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